UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,926	07/31/2003	Carlo Riccardi	RICCARDI=1A	7576

1444 7590 01/25/2006

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,926	RICCARDI, CARLO	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 4 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 11/17/2005 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-20 are pending. Applicant amended claims 3,4 and 19, and cancelled claims 1, 2, 5-16 and 20. The sections of 35 U.S.C. not included in this office action can be found in a previous office action. An action on the merits follows. Claims 3, 4 and 17-19 are currently under consideration.

Priority

In the prior action of 5/17/05 it was noted that parent application 09/403,861, issued as US Patent No. 6,833,348, did not provide an enabling disclosure for said mouse, a method of making or a method of using. Therefore the effective priority date for the claimed invention is its filing date of 7/31/2003. Since applicant has not traversed the basis of the examiner's determination it is presumed that they have acquiesced to this priority date.

Objections

The objections to claims 3, 4 and 17-18 under 37 CFR 1.75(c), as being of improper dependent form are withdrawn in view of applicant's amendments to the claims.

Drawings

The objection to the drawings under 37 CFR 1.83(a) because they fail to show the banding patterns as described in the specification is withdrawn in view of applicant's submission of replacement drawings.

Rejections under second paragraph of 35 U.S.C. 112:

The rejection of claims 3, 4 and 17-19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 112

The rejection of claims 3, 4 and 17-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants arguments.

The rejection of claims 3, 4 and 17-19 under 35 U.S.C. 112, first paragraph is maintained, because the specification, while being enabling for a transgenic mouse with a nucleic acid construct comprising an 874 bp mouse GILZ cDNA operably linked to a human CD2 promoter and a human CD2 locus control region integrated into its genome, wherein said mouse expresses the GILZ protein in its T-cell lineage at an elevated level, compared to a non-transgenic mouse, wherein the elevated level of GILZ protein expression results in a significant decrease in CD4.sup.+CD8.sup.+ double positive, and increases in CD4.sup.-CD8.sup.- double negative, CD8.sup.+ single positive cells, and the CD4.sup.+ subpopulation, compared with a non-transgenic mouse, and increased caspase 3 activation; a method of using said transgenic mouse for screening compounds having glucocorticoid-related effects, comprising administering a compound to said transgenic mouse and to a non-transgenic mouse and comparing the effects of

the compound on the two mice; and a method of making said transgenic mouse comprising transferring a nucleic acid construct comprising an 874 bp mouse GILZ cDNA operably linked to a human CD2 promoter and a human CD2 locus control region into a fertilized oocyte, transplanting said oocyte into a female mouse, allowing the zygote to develop to term, and selecting from the offspring a heterozygous transgenic mouse wherein the nucleic acid construct has integrated into its genome and the mouse expresses the GILZ protein in its T-cell lineage at an elevated level, compared to a non-transgenic mouse, breeding said heterozygous transgenic mouse to a wild type mouse to obtain F1 progeny heterozygous for said transgene and breeding a heterozygous male mouse from the F1 progeny with a heterozygous female mouse from the F1 progeny and selecting for a mouse homozygous for the transgene, does not reasonably provide enablement for a transgenic mouse with any nucleic acid construct comprising any GILZ cDNA from any species operably linked to any mammalian T-cell lineage specific promoter sequence, wherein said mouse expresses GILZ in its T cell lineage at an elevated level compared to a non-transgenic mouse and wherein the expression of GILZ results in any alteration of the thymocyte subset composition and caspase-3 activation, a method of using any such transgenic mouse for screening compounds having glucocorticoid-related effects, or a method of making any such transgenic mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 11/17/2005 have been fully considered but they are not persuasive. The previous office action identified the following issues of record: **1)** failure to enable any transgenic mouse comprising any mammalian T-cell specific promoter operably linked to any GILZ sequence; **2)** failure to provide guidance on a method of making any transgenic mouse; and **3)** failure to provide guidance on any mouse wherein GILZ expression resulted in the alteration of any thymocyte subset composition and of caspase 3 activation.

1 &2) The basis of issues **1** and **2** are closely related, and therefore will be treated together. Applicant argues that the specification is enabling as filed. Specifically that armed with the teachings of example 2 and the contemplated list of possible T-cell lineage specific promoters a practitioner in the art could make the claimed mouse using any T-cell lineage specific promoter. This not found to be persuasive. Applicant has described in example 2 the manufacture of a mouse with a very specific phenotype. Specifically, where the mouse has an elevated level of GILR protein expression results in a significant decrease in CD4.sup.+CD8.sup.+ double positive, and increases in CD4.sup.-CD8.sup.- double negative, CD8.sup.+ single positive cells, and the CD4.sup.+ subpopulation, compared with a non-transgenic mouse, and increased caspase 3 activation. The specification only provides guidance on a method of making said mouse with a transgene comprising an 874 bp mouse GILR cDNA operably linked to a human CD2 promoter and a human CD2 locus control region. There is no guidance on a method of making said mouse using any other T-cell lineage specific promoter. The method of making the claimed mouse, as set forth in claim 19 is carried out by random integration of the transgene into the genome. Transgene promoters and their operably linked gene do not function in isolation from the remaining genome. Instead, a transgene's expression

level and pattern of tissue expression is affected by its integration site, which can lead to repressed expression or leaky expression depending on the promoter used. The term T-cell lineage specific promoter encompasses the entire lck promoter system. This system contains a distal and proximal promoter, of which the proximal promoter contains a transcriptional repressor (Muise-Helmericks et al. (1995) J. Biol. Chem. 270:27538-27543; Abstract; pg. 27538, col. 1). This system regulates both the developmental and cell type expression of lck (pg. 27538, col. 1). Such a promoter system would not reasonably be predicated to produce the same disclosed phenotype as the instant mouse. Further, the specification discloses that the promoter and LCR of hCD2 were used to make the claimed mouse because they confer 3 important features to the hCD2-mGILR transgene: tissue specificity; cop-dependence; and position-independent expression (Specification pg. 89, Results). This a specific and clever system designed to overcome the problems with integration discussed above. The skilled practitioner would not predict that any other T-cell lineage specific promoter system, by itself, would reliably produce the claimed phenotype, since such a promoter would lack the hCD2 LCR.

The claims as presently drawn lack a defined phenotype for the claimed mouse. In absence of a defined phenotype or characteristic that is required for using the transgenic mouse, an artisan would not have known how to use the claimed mouse. The specification discloses that GO-TG mouse is used as a model to study the effects on T cell development due to constitutive GILR overexpression (Specification, pg. 90, section C). The phenotype of transgenic animals is affected by multiple factors other than the sequence of a transgenic construct; such as the specific site of transgene integration into the genome (positional effect), the level of expression, chromatin organization, and the pleiotropic effects of the transgene and interactions with other

gene products. Therefore the phenotype of any given transgenic mouse cannot be predicted based solely on the sequence of a transgenic construct. The claims, as presently drawn, encompass mice that over-express GILZ without any effect on T cell development. In other words, an artisan would not know how to use the claimed mouse in the absence of a phenotype.

Further, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the vector used, and the specific site of transgene integration into the genome (positional effect), for example, are all important factors in controlling the expression of a transgene in the production of transgenic mammals which exhibits a resulting phenotype. This observation is supported by Houdebine et al., who states that "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" {Houdebine et al. (2000) Transgenic Research 9:305-320; pg. 309, col. 2:The expression of transgenes}. Further, Houdebine et al. states that the potency of any transgene can only be estimated in transgenic mammals and the level of expression of transgenes in mice is not predictive of their levels in other mammals (pg. 310, col. 1, pgph 2). Finally, Houdebine et al. states that another well known problem with transgenesis is leaky expression of the transgene in various tissues in which the utilized promoter is not expected to work because of ectopic expression due to a position effect (pg. 310, col.1, pgph 3). See also Kolb et al., who states that "the expression of foreign genes in transgenic mammals is generally unpredictable as transgenes integrated at random after pro-nuclear injection into fertilized oocytes" because of inhibition by neighboring chromatin {Kolb et al. (1999) Gene 227:21-31; Abstract}. For the

reasons stated above and the problems cited in the art, mere recitation of possible promoters is not enough to provide enablement for any transgenic mouse containing a transgene comprising said promoter(s) and without a claimed distinct and reproducible phenotype. Therefore for the reason stated above and in the office action of 5/17/2005 the rejection is maintained over issues **1** and **2**.

3) Applicant has amended the claim to remove any defining phenotype from the claimed mouse. However, as stated above: The specification teaches that the claimed GO transgenic mouse is a model for studying GILZ overexpression in T-cell ontogeny (pg. 91). However, the claim lack a phenotype associated with the claimed mouse. Thus the artisan would not know how to use said mouse without a related phenotype. Amending the claims to include a fully supported and specific phenotype would be remedial.

No claims allowed

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
Patent Examiner
Art Unit 1632

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630